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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/393,795	09/10/1999	JOHN T. GRAY	CMCC693P2A	3301

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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/393,795	GRAY, ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,7-10,12-14,16-18,20,22-25,27-29,31-33 and 35-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-3,5,7-10,12-14,16-18,20,22-25 and 27-29* is/are allowed.

6)☒ Claim(s) *31-33 and 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 September 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 9/2/2003, in which nonelected claims were cancelled (claims 4, 6, 11, 15, 19, 21, 26, 30, 34 and 38-49) and in which claims were amended (claims 1, 5, 7-8, 12, 16, 20, 22-23, 27, 31 and 35). Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25, 27-29, 31-33, 35-37 are pending in the instant application.

Any rejection of record not addressed herein is withdrawn. Upon further review of the prior art, it is evident that the claims directed to a retroviral particle produced by applicants' methods are not free of the art (claims 31-33, 35-37). In short, the recited methods for making the claimed particles do not confer a structural/functional property that distinguishes the particles from those already taught in the art (see below). As these grounds for rejection were not necessitated by applicants' amendment of the claims, this action is not final.

Drawings

Applicants are reminded that the drawings were objected to by the Draftsperson on the PTO Form 948 mailed 2/15/2000 (Paper No. 8). A copy of the PTO Form 948 is attached to this action. In order to avoid abandonment, the drawing informalities noted in Paper No. 8, mailed on 2/15/2000, must now be corrected. Correction can only be effected in the manner set forth in the above noted paper. The requirement for corrected drawings will not be held in abeyance.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Each of the rejected claims is directed to a product-by-process claim reciting a HIV-derived retroviral particle having no viral accessory proteins produced by applicants three-plasmid system. The novelty of applicants' three-plasmid packaging system is (i) the lack of any sequences in the packaging cells encoding the retroviral accessory proteins, any Rev response element (RRE) or any constitutive transport element (CTE) on the plasmid encoding *gagpol*, and (ii) the *gagpol* sequences are codon-optimized for expression. The art cited below is applicable to the rejected claims in that the methods recited in the rejected claims for making the claimed particles do not confer a structural/functional characteristic that distinguishes the particles from the prior art. For example, the *gagpol* sequences are not intended for incorporation into the resulting viral particle in practicing the recited methods or in the methods of the prior art. Therefore, codon optimization does not affect the novelty of the particle produced by the recited methods of the rejected claims because the *gagpol* sequences are not present in the particles produced. Similarly, the particles produced by the methods used in the prior art cited below do not result in the incorporation of any of the retroviral accessory proteins (e.g. vif, vpr, vpu, nef, tat or rev) for reasons indicated below. Thus, the particles produced by the prior art methods read on the rejected claims.

Claims 31-32, 35-36 are rejected under 35 U.S.C. 102(a) as being anticipated by Kim et al (Journal of Virology, January 1998, Vol. 72, No. 1, pages 811-816; see the entire document) as evidenced by Luciw (Paul Luciw, Fundamental Virology, 3rd Ed., Fields, Knipe and Howley editors-in-chief, Lippencott-Raven, Philadelphia-New York, 1996, Chapter 27, page 850) . **This is a new rejection.**

Kim et al teach a 3 vector system for producing HIV packaging cells useful for the characterization of the minimal requirements for lentiviral accessory proteins in HIV particle production in the packaging cells (e.g. Abstract). For example, in certain experiments, 293T cells were infected with (i) a gagpol expression construct (i.e. pGP-RRE3) that expresses a *gagpol* transcript comprising a Rev response element (RRE), (ii) an expression construct expressing the vesicular stomatitis virus G envelope protein (VSV G) and (iii) a "gene transfer" construct comprising a DNA sequence of interest (i.e. *lacZ*) and lentiviral cis-acting sequences required for packaging, reverse transcription and integration. Resulting viral particle titers were determined on 293T cells by counting the number of blue colonies and ranged from ~3 X 10^5 LFU/ml to ~8 X 10^5 LFU/ml (e.g. Tables 1 and 3).

The viral particles produced using these methods would not be expected to comprise any of the accessory proteins. For example, the only regulatory proteins expressed in these examples are ones that are not incorporated into the virion particle. Extrinsic evidence this is the case is provided by the teachings of Luciw. Luciw teaches that of the accessory proteins, only Vpr and Vpx are packaged into virions and that the other accessory/regulatory proteins (i.e. Vif, Vpu, Nef, Rev, Tat) are not detectable in virion particles (e.g. legend for Figure 4).

Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claims 31 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Srinivasakumar et al (Journal of Virology, August 1997, Vol. 71, No. 8, pages 5841-5848; see the entire reference) as evidenced by Luciw (Paul Luciw, Fundamental Virology, 3rd Ed., Fields, Knipe and Howley editors-in-chief, Lippencott-Raven, Philadelphia-New York, 1996, Chapter 27, page 850) . **This is a new rejection.**

Srinivasakumar et al examine the effect of viral regulatory protein expression on gene delivery for HIV-1 type vectors produced by stable packaging cell lines (e.g. Abstract). Srinivasakumar et al teach a 3 or 4 vector system (e.g. Figures 1A and 1B) for generating packaging cells analogous to that recited in the rejected claims except that the *gagpol* vector comprises a RRE or CTE element operatively linked to the gagpol sequence and the *gagpol* sequences are not codon optimized. The packaging cells taught by Srinivasakumar et al (i.e. B4.14, 5BD.1, 2A.22) do not appear to express the accessory proteins known in the art to be packaged into the virion (i.e. Vpr and Vpx). Each of the packaging cell lines was capable of packaging a gene transfer vector (e.g. pTR167; Figure 3, Table 1) into infective viral particles (e.g. ~1.8 X 10^3 CFU/ml to 9 X10^3 CFU/ml; Table 1).

The viral particles produced using these methods would not be expected to comprise any of the accessory proteins. For example, the only regulatory proteins expressed in these examples (e.g. Rev, Tat, Nef) are ones that are not expected to be incorporated into the virion particle. Extrinsic evidence this is the case is provided by the teachings of Luciw. Luciw teaches that of the accessory proteins, only Vpr and Vpx are packaged into virions and that the other accessory/regulatory proteins (i.e. Vif, Vpu, Nef, Rev, Tat) are not detectable in virion particles (e.g. legend for Figure 4).

Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 31-33, 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al (Journal of Virology, January 1998, Vol. 72, No. 1, pages 811-816; see the entire document) or Srinivasakumar et al (Journal of Virology, August 1997, Vol. 71, No. 8, pages 5841-5848; see the entire reference) in view of Naldini et al (Science, April 1992, Vol. 272, page 263-267; see the entire reference).

The teachings of Kim et al or Srinivasakumar et al are outlined above and are applied as before, except:

Kim et al do not teach the use of the Moloney leukemia virus envelope protein (MLV Env). Srinivasakumar et al do not teach the use of the MLV envelope protein or the vesicular stomatitis virus envelope protein (VSV G) in their methods.

Naldini et al teach an analogous 3-vector approach for generating recombinant retroviral particles comprising a gene transfer vector (e.g. Figure 1). Naldini et al teach that the use of the MLV or VSV G envelope proteins for pseudotyping the recombinant viral particles produced by their methods in order to increase the range of target cells that can be infected by the particles produced by their system.

It would have been obvious to one of ordinary skill in the art at the time of applicants' invention to modify the teachings of either of the two primary references to incorporate either of

the two envelope proteins taught by Naldini et al because (i) each of the three references teach it is within the skill of the art to produce viral particles using an analogous, multi-vector system to separately express the *gagpol* and *env* sequences in order to produce lentiviral virions comprising a desired gene transfer construct, and (ii) because Naldini et al teach it is within the skill of the art to use non-HIV envelope proteins to increase the range of cell types that can be infected by the produced virions. One would have been motivated to make such a modification in order to increase the host cell range that could be infected by the different types of virions comprising a different envelope. For example, one could use the virions made by the combined teachings of the different references to study the contribution that the accessory proteins make in different cell types infectable by the different virions. Absent any evidence to the contrary, there would have been a reasonable expectation of success in modifying the teachings of Kim et al or Srinivasakumar et al to include the teachings of Naldini et al with regard to heterologous envelope proteins to produce recombinant HIV-derived particles comprising the MLV or VSV G envelope proteins.

Conclusion/Examiner's Notes

Claims 1-3, 5, 7-10, 12-14, 16-18, 20, 22-25 and 27-29 are allowed. Claims 31-33 and 35-37 are rejected.

It is noted that there is no apparent literal support in the specification as filed for a negative limitation in the rejected claims that the gene transfer vector (i.e. the third vector as recited in the rejected claims) does not comprise a RRE or CTE.

Kotsopoulou et al (Journal of Virology, May 2000, Vol. 74, No. 10, pages 4839-4952) was cited in applicants response filed 3/17/2003. This reference has not previously been made officially of record such that it will be printed on the face of any patent issued from the instant application. For this reason, the reference has been cited on the attached PTO-892.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

Ggl

GERRY LEFFERS
PRIMARY EXAMINER